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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LANDAU, SHARMILA GOLLAMUDI	
ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/886,296	TARARA ET AL.	
	Examiner	Art Unit	
	Sharmila Gollamudi Landau	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Amendments/Remarks and the Information Disclosure Statement filed 8/30/07 is acknowledged. Claims **56-102** are pending in this application. Claims 1-56 stand cancelled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 57-77, 80-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5,855,913) in view of Unger (6,120,751) as evidenced by 5,776,488. Note US '488 is only relied upon to show the inherent property claimed in claims 72 and 95.

Hanes et al teach aerodynamically light particles for drug delivery to the pulmonary system. The particles have a tap density of less than 0.4 g/cm3, aerodynamic diameter of 3 microns (see column 9, line 45-50), and a mass mean diameter (geometric diameter) between 5 to 30 microns. See abstract, See column 9, lines 26-45, and claim 1. Claim 3 teaches a tap density of less than 0.1 g/cm3. Table 2 teaches the porous microparticles with DPPC

(phospholipids) have a density of 0.30 g/cm3. It should be noted that Hanes teaches tap density is a standard measure of the envelope mass density (bulk density) on column 9, lines 5-6. On column 14, lines 36-40, Hanes teaches the bulk density is estimated by tap density measurements.

Hanes teaches the presence of irregular surface structure, or pores or cavities within the particle (this reads on instantly claimed "hollow microstructure") contributes to the aerodynamic lightness. Hanes also teaches the irregular surface texture and porous structure also contributes to the low tap density and manipulation of these features permits the delivery of larger particle envelope volumes into the lungs (col. 9, lines 10-25). Porosity and surface roughness can be increased by varying the inlet and outlet temperatures, among other factors. See column 12, lines 10-13. The aerodynamically light particles may be fabricated to provide a particle sample with a preselected size distribution. For example, greater than 30%, 50%, 70%, or 80% of the particles in a sample can have a geometric diameter within a selected range of at least 5 microns. The particles contain surfactants such as DPPC (instant gel to liquid temperature; see US 5,776,488 as art of interest) and the microstructures are taught to encapsulate active agents, which allows the active to remain protected (col. 10, lines 37-50 and examples). Note that DPPC is a zwitterionic lipid. The particles can also be co-delivered with larger carrier particles, not carrying a therapeutic agent, having, for example, a mean diameter ranging between about 50 microns and 100 microns. See column 4, lines 12-15.

Biodegradable polymer, copolymers, or a blend may be utilized. Hanes teaches the use of polyglycolic acid and polylactic acid with a surfactant (DPPC) may be utilized and the polyester may also have a charged or functionizable groups such as amino acids. Other polymers taught

are acrylic acids and methacrylic acids and polyvinyl compounds may be used to make the microsphere. See column 5, line 49 to column 6, line 27. Further, the particles may be formed into microspheres by various methods including but not limited to **coacervation (note a coacervate is a spherical aggregation of lipid molecules)**, interfacial polymerization, etc. (note col. 6). Instant therapeutic agents including insulin, growth hormones, etc. are taught on column 10, lines 4-30.

Hanes teaches aerodynamically light PEG particles were prepared by spray drying using 5 g PEG (MW 15,000-20,000, Sigma) and the surfactant such as DPPC may be incorporated into the polymer solution prior to particle formation, or optionally the particles can be ionically or covalently coated by surfactant on the particle surface after particle formation, or the surfactant may be absorbed onto the particle surface. See column 13, lines 1-25. Note that when DPPC is incorporated into the polymer solution to form the particles, DPPC is part of the structural matrix.

Hanes et al do not teach the use of calcium in the structural matrix.

Unger teaches charged lipids and their use for drug delivery, targeted delivery, etc. See abstract. Unger teaches prior art studies have described the effects of calcium and other multivalent cations on membrane asymmetry, lipid distribution, vesicle size, aggregation and fusion. The general consensus exists that multivalent cations, such as calcium and magnesium, in the external environment of phospholipid vesicles cause the structures to aggregate into larger, multilamellar structures and promotes fusion. Unger's composition comprises a charged lipid, a counter ion, a lipid covalently bonded to a polymer, and a bioactive agent. See column 2, lines 20-30. The composition is in the form of a vesicle including liposomes and micelles, which can

be solid or porous. See column 4, lines 19-45. The vesicles preferably have diameters of less than about 30 microns and more preferably less than about 12 microns. See column 68, lines 1-6. The charged lipid may be anionic (i.e., negatively charged, that is, carrying a net negative charge) or cationic (i.e., positively charged, that is, carrying a net positive charge). See column 11, lines 5-10. A cationic counter ion is used to form the compositions. Preferred cations are **calcium**, magnesium, and zinc, and paramagnetic cations such as manganese and gadolinium. Most preferably the cation is calcium. See column 12, lines 1-5. Specifically, example 2 teaches the composition comprising instantly claimed dipalmitoylphosphatidylcholine (**DPPC**), dipalmitoylphosphatidic acid (DPPA), dipalmitoylphosphatidylethanolamine-polyethylene glycol-5,000 (DPPE-PEG5,000), and calcium chloride. Example 13 discloses lyophilizing the composition of example 2 to yield a dry powder. Unger teaches the lipid covalently bonded to a polymer (e.g., DPPE-PEG-5,000) causes compaction of the size of the composition in the presence of a counter ion, such as calcium, when compared to the corresponding compositions that do not contain a counter ion. The compaction effect caused by the lipid covalently bonded to the polymer is most notable when the counter ion is added at the initial incubation of the lipid mixture. Increasing the amount of the lipid covalently bonded to a polymer allows the composition to stabilize in the presence of a counter ion. When the lipid covalently bonded to the polymer is present in an amount less than about 5%, the composition is generally unstable and may precipitate. See column 10, lines 50-55. Unger discloses the lipid composition is useful for delivering bioactive agents to a patient's lungs. For pulmonary applications, dried or lyophilized powdered compositions are administered via an inhaler.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hanes and Unger and utilize calcium in the microstructures of Hanes. One would have been motivated to utilize calcium in the formation of Hanes's particles since Unger teaches the use of a cations such as calcium promotes fusion of the phospholipids and stabilizes compaction of phospholipid-polymer containing particles, specifically in a PEG-phospholipid particle. Further, a skilled artisan would have expected the same stabilizing effect in Hanes's particles since Hanes also teaches a particle comprising PEG and a phospholipid.

With regard to the claims 4-5 (porosity), claims 6-7 (pore size), and claim 13 (shell thickness), although Hanes does not specify the porosity in terms of weight percent as instantly claimed, specify the pore size, or the shell thickness, it is the examiner's position that the Hanes would have a similar porosity, pore size, and shell thickness as instantly claimed for the following reason: Hanes teaches a substantially similar particle with instant bulk density (measured by tap density), instant geometric diameter, and instant aerodynamic diameter. Thus, "when a structure recited in the reference is substantially identical to that of the claims, claimed properties are presumed to be the inherent". See MPEP 2112.01. Further, Hanes teaches the porous and light nature of the microstructure contributes to the properties such as the low tap density of the particle and Hanes teaches the same density as claimed; thus the pore size and porosity must be similar as instantly claimed. Further, since the shell thickness also would contribute to the density of the particles and the prior art teaches the same density as claimed, it is the examiner's position that the prior art would have the same shell thickness as claimed. It should be noted that the examiner has provided a rationale as to why Hanes's particle would

have the same or similar porosity, pore size, and shell thickness; thus the burden has shifted to the applicant to provide evidence to the contrary. See MPEP 2112.

Furthermore, assuming arguendo that Hanes's porosity, pore size, and shell thickness are not the same as instantly claimed, the manipulation of these parameters is considered prima facie obvious to one of ordinary skill in the art since Hanes provides the guidance in which the various factors can be manipulated (column 9 and examples) to yield the desired property. For instance, Hanes teaches manipulating the outlet and inlet temperature when making the particles to manipulate the porosity. Further, Hanes teaches the manipulation of surface roughness (porosity), diameter, and tap density, determine the delivery site of the particles in the lungs (lower lung region or upper lung region). (col. 8, lines 19-68 and column 9). Therefore, a skilled artisan would have been motivated to look at the guidance of Hanes and manipulate the above factors and fabricate the microstructure according to the lung region to be targeted.

Regarding the claim language of 58 and 81, Note MPEP 2111.03: The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." The examiner also points out that Hanes teaches the particles may be made of the surfactant, i.e. phospholipids.

Response to Arguments

Applicant argues that Hanes teaches particles made from organic materials such as ceramic or polymers. Applicant argues that Hanes teaches DPPC on the surface of the particles

to reduce tendency of the particles to agglomerate due to electrostatic interactions. Thus, applicant argues that Hanes does not teach a structural matrix. Applicant argues that Hanes briefly mentions that the particles can be made from surfactants entirely but this is not enabled. Applicant argues that Hanes does not teach the use of calcium and Unger does not cure this deficiency. Applicant argues that the instant claims are directed to discrete particulate microstructures that have decreased aggregation and Unger teaches cations such as calcium causes aggregation of phospholipids vesicles. Applicant argues that such an aggregation teaches away from the instantly claimed inhaleable powder composition comprising a plurality of discrete particulate microstructures that are substantially not aggregated in the powder. Applicant argues that column 1, line 50 to column 2, line 9 supports applicant's assertion that calcium causes aggregation and fusion and thus one would not have been motivated to look to Unger. Applicant argues that the examiner's cited passages support applicant's position. Applicant argues that Unger teaches a lipid covalently bound to a polymer and the instant claims are not directed to a lipid covalently bound to a polymer.

Applicant's arguments filed 8/30/07 have been fully considered but they are not persuasive. Firstly, The examiner points out that the instant claim language, i.e. comprising, does not exclude Hanes' or Unger's polymers. The claims only require phospholipids in the structural matrix, which is clearly taught by both references.

Secondly, the directs applicant's attention to column 5, lines 15-25:

> As used herein, a particle "incorporating a surfactant" refers to a particle with a surfactant on at least the surface of the particle. The surfactant may be incorporated throughout the particle and on the surface during particle formation, or may be coated on the particle after particle formation. The surfactant can be coated on the particle surface by adsorption, ionic or covalent attachment, **or physically "entrapped" by the surrounding matrix. The surfactant can be, for example, incorporated into controlled release particles, such as polymeric microspheres.**

Therefore, Hanes suggests incorporating the phospholipids into the polymeric matrix. Also note example 3 wherein Hanes teaches entrapped DPPC within the microspheres.

The examiner further directs applicant's attention to column 5, lines 58-60:

Optionally the **particles may be formed of the surfactant** plus a therapeutic or diagnostic agent.

Applicant argues that Hanes is not enabled for this embodiment; however applicant does not provide any support for this argument. The mere fact that Hanes does not exemplify this embodiment does not mean it is not enabled. The examiner directs applicant's attention to MPEP 2121: PRIOR ART IS PRESUMED TO BE OPERABLE/ ENABLING. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). Also see MPEP 716.07. The examiner further points to MPEP 2121.01 (II): "Even if a reference discloses an inoperative device, it is prior art for all that it teaches." Clearly, Hanes teaches the particles may be made of surfactants, i.e. phospholipids.

The examiner relies on Unger to cure Hanes' deficiency in the teaching of calcium.

Unger teaches on column 68, lines 1-6 that the vesicles preferably have diameters of less than about 30 microns and more preferably less than about 12 microns (note this refers to the geometric diameter). Further, Unger teaches the vesicles for inhalation from dry powder inhalers. The instant specification discloses that a size greater than 50 microns tends to aggregate and clog the valve or orifice of the inhaler. Thus, clearly a problem of clogging the valve of an inhaler is not encountered since Unger teaches the same particle size as claimed by applicant.

Secondly, the examiner notes column 1, beginning at line 50 to column 2, line 9; however this passage refers to the *prior art*. Unger clearly teaches, "The present invention is directed to,

among other things, the development of new and improved drug and contrast media delivery systems that overcome the problems associated with the prior art." Unger teaches the use of the polymer bound to the lipid overcomes the prior art problems, which will be discussed below.

Further as noted by applicant, Unger teaches calcium and magnesium in the "external environment" of phospholipids vesicles causes the structures to aggregate into larger, multilamellar structures to promote fusion *between* vesicles. However, Unger invention is directed to the calcium ions as part of the structural matrix, i.e. part of the vesicle itself, and not part of the *external* environment. Thus, this property of calcium to promote fusion as used by Unger is utilized to "fuse" the lipid components to form a stable vesicle. Unger's teachings are not directed to placing the formed particles in a solution or "environment" containing calcium, which would cause the aggregation of the individual lipid vesicles. As taught and discussed by Unger on column 1 and 2, during storage the drug tends to leak out the liposomes and thus Unger uses the calcium ion to promote fusion of the lipid components within the vesicle itself. Again examiner points out that Unger is teaching the use of calcium to fuse the lipid components to form the particle itself. Thus, the "aggregates" of these lipids form the vesicle and are within the specified particle size of less than 30 microns and preferably less than 12 microns as taught by Unger. Thus, the concentration of calcium used determines the size the vesicle desired. Thus, one would use the desired amount of calcium to provide the desired aggregation or fusion of the lipid components to obtain the desired particle size. It should be noted that both Unger and Hanes teach particles with a geometric diameter of less than 30 microns. Further, it should be noted that Hanes teaches coacervation to make the particles. Coacervate is a spherical aggregation of lipid molecules. Note the definition provided with the office action.

Applicant argues that the examiner has used hindsight and Hanes teaches away from the aggregation of vesicles.

The examiner acknowledges that Hanes teaches away from aggregation of the *individual* vesicles. Thus, one would not have been motivated to have calcium in the external environment, which would cause the individual vesicles to clump. Hanes also teaches the use of a surfactant to prevent clumping between vesicles. However, Unger teaches and uses the invention pertains to calcium *within* the particle matrix to enforce and stabilize the individual vesicle itself.

On column 10, lines 33-50m Unger teaches:

> Without intending to be bound by any theory of the invention, in the compositions of the present invention, the counter ions (calcium) form salt bridges which crosslink the charged lipids to form aggregates or multilamellar vesicles. The aggregates or multilamellar vesicles may be referred to as cochleates, which may be in the form of a tubule or a spiral. The crosslinking of the counter ions may be noncovalent and may generally be considered an ionic or electrostatic interaction. The lipid covalently bonded to the polymer stabilizes the compositions so that they from **well-defined vesicles**. If the lipid covalently bonded to the polymer is not used in the compositions of the present invention, the counter ions cause the charged lipid species to form amorphous lipid clumps. In many cases, the lipid clumps may take the form of, for example, condensed lipid bilayers, but the lipid clumps do not form stable vesicles with size distributions suitable, for example, for intravenous injection.
>
> The lipid covalently bonded to a polymer (e.g., DPPE-PEG-5,000) causes compaction of the size of the composition in the presence of a counter ion, such as Ca.sup.2+ (FIGS. 2B, 3B and 4B), when compared to the corresponding compositions that do not contain a counter ion (FIGS. 2A, 3A and 4A).

Further, from the above disclosure, it is noted that 1) the term "aggregate" as used by Unger means group of lipids to *form* multilamellar vesicle or liposome; 2) Unger's particles discrete particles; and 3) Unger utilizes a polymer which is bound to the lipid bound to prevent the problems typically associated with calcium as discussed by Unger in columns 1 to 2. Specifically, Unger uses DPPE-PEG. Thus, Unger clearly teaches an improvement of the prior art vesicles. Hanes also utilizes a lipid conjugated to a polymer, i.e. DPPC-PEG. Thus, the motivation to further utilize a cation such as calcium is to provide stability to the vesicle and promote fusion of the individual lipids within the particle.

The examiner further points to column 4, lines 45-54 to further differentiate applicant's use of the term "aggregate" and Unger's use of the term aggregate:

> "Liposome" refers to a generally spherical or spheroidal cluster or aggregate of amphipathic compounds, including lipid compounds, typically in the form of one or more concentric layers, for example, monolayers, bilayers or multi-layers. They may also be referred to herein as lipid vesicles. The liposomes may be formulated, for example, from ionic lipids and/or non-ionic lipids. Liposomes formulated from non-ionic lipids may be referred to as niosomes. Liposomes formulated, at least in part, from cationic lipids or anionic lipids may be referred to as cochleates.

It is emphasized that Unger utilizes the term to refer to a collection of lipid compounds that form (aggregate) a multilamellar vesicles or liposome and not to define it as collection of particles clumped together. Summarily, the aggregation caused by calcium refers to calcium promoting fusion of the individual phospholipids to form a vesicles rather than fusion *between* the vesicles. Further note Figure 1A which demonstrates calcium's role in forming vesicles.

Applicant argues that Hanes teaches dissolving the polymer in an organic solvent and suspended in an aqueous medium comprising a surface-active agent to form an emulsion, which is followed by evaporating the solvent to form the particles. Applicant argues that the addition of calcium for aggregation purposes might form particles larger than described by Hanes.

Firstly, the examiner points that Unger teaches the same size as taught by Hanes. Both Unger and Hanes teach particles with a geometric diameter of less than 30 microns. Secondly, the examiner points to column 64 of Unger wherein Unger also teaches the use of solvent evaporation to form particles. Further, both references teaches the method of making the particles is not critical and teaches different methods of making the particles. Secondly, Unger also teaches the use of surfactants (surface active agents) as stabilizing agents to reduce surface tension and both Hanes and Unger teach PEG-phospholipid based particles. Further, both Hanes and Unger teaches the similar particle size for inhalation as discussed above. Thus, the use of

calcium in Hanes's particles would also have the same effect as taught by Unger, i.e. to promote fusion *between* the individual phospholipids to form a well-defined vesicle. Again, the concentration of calcium used determines the size of the vesicle obtained. Thus, one would use the desired concentration of calcium to provide the desired particle size. Lastly, the examiner points out that Hanes teaches the particles may be made of the phospholipids and active. See claim 1 and column 5, lines 58-60. Thus, one would expect that if a skilled artisan followed Hanes' suggestion of preparing particles was made from the surfactant, i.e. phospholipids, the calcium would still act to fuse the phospholipids to form a vesicle. Again it should be noted that both Unger and Hanes teach particles with a geometric diameter of less than 30 microns.

Applicant argues that the limitation that the phospholipid comprises a gel to crystal transition temperature of greater than 40 degrees Celsius is not disclosed.

The examiner points out that Hanes teaches the same phospholipids and this limitation is an inherent feature of the claimed phospholipids. Thus, the prior art need not recognize every inherent property of an element to read on the claim. Further, the examiner provides US 5,776,488 as art of interest wherein Mori et al discloses DPPC has a transition temperature of 42 degrees Celsius. See column 3, lines 40-45. Applicant has not addressed this.

Claims 78 and 101 are under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Unger (6,120,751) in further view of Igarashi et al (4201774).

The detailed teaching of Hanes and Unger have been set forth above. Hanes et al teach dry powder inhaler compositions. Hanes teaches several active agents including antibiotics in the composition. Unger teaches the use of calcium to stabilize the phospholipids.

Hanes does not teach the specific use of aminoglycoside antibiotic.

Igarashi et al teaches aminoglycoside antibiotics for the treatment of gram-positive and gram-negative bacteria.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the instant medicament in Hanes et al's composition. One would be motivated to do so since the instant antibiotics treats gram-positive and gram-negative bacteria and depending on the patient's requirement, the appropriate drug is used. One would have expected similar results since Hanes teaches the suitability of antibiotics as the active agent. Therefore, the selection of a particular drug for use in the composition is considered prima facie obvious since the selection depends on the symptoms and disease being treated.

Response to Arguments

Applicant argues that Hanes does not teach calcium or the instant active agent. Applicant argues Unger teaches calcium causes aggregation and the instant specification teaches away from aggregation. Applicant argues Igarashi does not teach particulate microstructures comprising calcium, lipids, and an active agent. Thus, applicant argues the rejection is improper.

Applicant's arguments filed 8/30/07 have been fully considered but they are not persuasive. The teachings of Hanes and Unger have been discussed above. The examiner notes that Igarashi does not teach the instant microstructures; however the examiner points out that Igarashi is not relied for its teaching of the microstructure since the combination of Hanes and Unger are not deficient in this sense. Igarashi teaches the use of the instant active agent for treating gram positive and gram-negative infections. Thus as set forth in the rejection, a skilled artisan would have been motivated to utilize the instant drug to treat a gram positive or negative bacterial infection.

Claims 79 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Unger (6,120,751) in further view of Benson et al (5,006,343).

The detailed teaching of Hanes and Unger have been set forth above. Hanes et al teach dry powder inhaler compositions. Hanes teaches several active agents including antibiotics in the composition. Unger teaches the use of calcium to stabilize the phospholipids.

Hanes does not teach the specific use of fungicides.

Benson et al teach pulmonary administration of active agents to treat pulmonary diseases. Suitable drugs that may be administered for lung specific disease include fungicides. See column 10, lines 33-45.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a fungicide in Hanes et al's composition. One would be motivated to do so since Benson et al teach the use of array of medications including fungicides that are useful for treating lung diseases. Therefore, the selection of a particular drug for use in the composition is considered prima facie obvious since the selection depends on the symptoms and disease being treated.

Response to Arguments

Applicant argues that Hanes does not teach calcium or the instant active agent. Applicant argues Unger teaches calcium causes aggregation and the instant specification teaches away from aggregation. Applicant argues Benson does not teach particulate microstructures comprising calcium, lipids, and an active agent. Thus, applicant argues the rejection is improper.

Applicant's arguments filed 8/30/07 have been fully considered but they are not persuasive. The teachings of Hanes and Unger have been discussed above. The examiner notes that Benson does not teach the instant microstructures; however the examiner points out that Benson is not relied for its teaching of the microstructure since the combination of Hanes and Unger are not deficient in this sense. Benson teaches the use of the instant active agent for treating lung diseases. Thus as set forth in the rejection, a skilled artisan would have been motivated to utilize the instant drug to treat a certain lung diseases.

Claims 57-77, 80-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5,855,913) in view of Mathiowitz et al (6,248,720) or Cohen et al (5149543) respectively as evidenced by 5,776,488. Note US '488 is only relied upon to show the inherent property claimed in claims 72 and 95.

Hanes et al teach aerodynamically light particles for drug delivery to the pulmonary system. The particles have a tap density of less than 0.4 g/cm3, aerodynamic diameter of 3 microns (see column 9, line 45-50), and a mass mean diameter (geometric diameter) between 5 to 30 microns. See abstract, See column 9, lines 26-45, and claim 1. Claim 3 teaches a tap density of less than 0.1 g/cm3. Table 2 teaches the porous microparticles with DPPC (phospholipids) have a density of 0.30 g/cm3. It should be noted that Hanes teaches tap density is a standard measure of the envelope mass density (bulk density) on column 9, lines 5-6. On column 14, lines 36-40, Hanes teaches the bulk density is estimated by tap density measurements.

Hanes teaches the presence of irregular surface structure, or pores or cavities within the particle (this reads on instantly claimed "hollow microstructure") contributes to the aerodynamic

lightness. Hanes also teaches the irregular surface texture and porous structure also contributes to the low tap density and manipulation of these features permits the delivery of larger particle envelope volumes into the lungs (col. 9, lines 10-25). Porosity and surface roughness can be increased by varying the inlet and outlet temperatures, among other factors. See column 12, lines 10-13. The aerodynamically light particles may be fabricated to provide a particle sample with a preselected size distribution. For example, greater than 30%, 50%, 70%, or 80% of the particles in a sample can have a geometric diameter within a selected range of at least 5 microns. The particles contain surfactants such as DPPC (instant gel to liquid temperature; see US 5,776,488 as art of interest) and the microstructures are taught to encapsulate active agents, which allows the active to remain protected (col. 10, lines 37-50 and examples). Note that DPPC is a zwitterionic lipid. The particles can also be co-delivered with larger carrier particles, not carrying a therapeutic agent, having, for example, a mean diameter ranging between about 50 microns and 100 microns. See column 4, lines 12-15.

Biodegradable polymer, copolymers, or a blend may be utilized. Hanes teaches the use of polyglycolic acid and polylactic acid with a surfactant (DPPC) may be utilized and the polyester may also have a charged or functionizable groups such as amino acids. Other polymers taught are acrylic acids and methacrylic acids and polyvinyl compounds may be used to make the microsphere. See column 5, line 49 to column 6, line 27. Further, the particles may be formed into microspheres by methods such as coacervation, interfacial polymerization, solvent evaporation, spray drying, and other methods known to those skilled in the art. (note col. 6). Hanes teaches methods of making the microspheres can include Mathiowitz's teachings. See

Instant therapeutic agents including insulin, growth hormones, etc. are taught on column 10, lines 4-30.

Hanes teaches aerodynamically light PEG particles were prepared by spray drying using 5 g PEG (MW 15,000-20,000, Sigma) and the surfactant such as DPPC may be incorporated into the polymer solution prior to particle formation, or optionally the particles can be ionically or covalently coated by surfactant on the particle surface after particle formation, or the surfactant may be absorbed onto the particle surface. See column 13, lines 1-25.

Hanes et al do not teach the use of calcium in the structural matrix.

Mathiowitz teaches polymeric microparticles for administration by inhalation. See abstract and column 4, lines 10-42. Mathiowitz teaches making nanospheres and microspheres in the range of 10nm to 10 microns. See column 7, lines 50-55.Various biodegradable polymers including the polymers taught by Hanes. See column 11, lines 30-50 and Table 1. Mathiowitz teaches the bioadhesive properties of a polymer are enhanced by incorporating a metal compound into the polymer to enhance the ability of the polymer to adhere to a tissue surface such as a mucosal membrane. Metal compounds which enhance the bioadhesive properties of a polymer preferably are water-insoluble metal compounds, such as water-insoluble metal oxides and hydroxides. The water-insoluble metal compounds, such as metal oxides, can be incorporated by one of the following mechanisms: (a) physical mixtures which result in entrapment of the metal compound; (b) ionic interaction between metal compound and polymer; (c) surface modification of the polymers which would result in exposed metal compound on the surface; and (d) coating techniques such as fluidized bead, pan coating or any similar methods known to those skilled in the art, which produce a metal compound enriched layer on the surface

of the device. The water-insoluble metal compounds can be derived from metals including **calcium**, iron, copper, zinc, cadmium, zirconium and titanium. See column 13, lines 20-51.

Cohen et al teach a method of making microspheres. The method is based on the use of water-soluble polymers with charged sides that are crosslinked with multivalent cations (abstract). Suitable polymers that are reacted with cations are polyacrylic acids, polymethacrylic acid, PCPP, polyvinyl compounds, etc (col. 4, lines 1-5). The cations taught are calcium, copper, magnesium, etc (col. 6, line 22). A typical example for microsphere preparation utilizes polymer and calcium chloride concentrations of 2.5% and 7.5% (w/v). Microspheres are prepared by spraying an aqueous solution of polymer containing the entity of interest, using a droplet-forming apparatus.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hanes and Mathiowitz and utilize calcium in the microstructures of Hanes. One would have been motivated to utilize calcium in the formation of Hanes's particles since Mathiowitz teaches the use of water-insoluble metal compounds derived from calcium, iron, copper, etc, enhance bioadhesive properties of the polymer to allow the microspheres to adhere to tissue surface such as mucosal surfaces. Therefore, a skilled artisan would have been motivated to add a compounds such as calcium to increase the bioadhesive properties of the microparticles. Moreover, a skilled artisan would have reasonably expected success since Hanes teaches polymeric-phospholipid microparticles for inhalation and thus one would have desired to increase the adherence of the particles to the respiratory mucosa.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hanes and Cohen since Cohen teaches the method of

making microspheres through interfacial polymerization using cations such as calcium. One would be motivated to do so with the expectation of similar results since Hanes teaches the use of polymers with charged sides such as polyacrylic acids, etc. and teaches that any process of making the microsphere is suitable including interfacial polymerization.

With regard to the claims 4-5 (porosity), claims 6-7 (pore size), and claim 13 (shell thickness), although Hanes does not specify the porosity in terms of weight percent as instantly claimed, specify the pore size, or the shell thickness, it is the examiner's position that the Hanes would have a similar porosity, pore size, and shell thickness as instantly claimed for the following reason: Hanes teaches a substantially similar particle with instant bulk density (measured by tap density), instant geometric diameter, and instant aerodynamic diameter. Thus, "when a structure recited in the reference is substantially identical to that of the claims, claimed properties are presumed to be the inherent". See MPEP 2112.01. Further, Hanes teaches the porous and light nature of the microstructure contributes to the properties such as the low tap density of the particle and Hanes teaches the same density as claimed; thus the pore size and porosity must be similar as instantly claimed. Further, since the shell thickness also would contribute to the density of the particles and the prior art teaches the same density as claimed, it is the examiner's position that the prior art would have the same shell thickness as claimed. It should be noted that the examiner has provided a rationale as to why Hanes's particle would have the same or similar porosity, pore size, and shell thickness; thus the burden has shifted to the applicant to provide evidence to the contrary. See MPEP 2112.

Furthermore, assuming arguendo that Hanes's porosity, pore size, and shell thickness are not the same as instantly claimed, the manipulation of these parameters is considered prima facie

obvious to one of ordinary skill in the art since Hanes provides the guidance in which the various factors can be manipulated (column 9 and examples) to yield the desired property. For instance, Hanes teaches manipulating the outlet and inlet temperature when making the particles to manipulate the porosity. Further, Hanes teaches the manipulation of surface roughness (porosity), diameter, and tap density, determine the delivery site of the particles in the lungs (lower lung region or upper lung region). (col. 8, lines 19-68 and column 9). Therefore, a skilled artisan would have been motivated to look at the guidance of Hanes and manipulate the above factors and fabricate the microstructure according to the lung region to be targeted.

Regarding the claim language of 58 and 81, Note MPEP 2111.03: The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." The examiner also points out that Hanes teaches the particles may be made of the surfactant, i.e. phospholipids.

Claims 57-77, 80-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5,855,913) in view of Papahadjopoulos et al (Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biophysics, 394 (1975), 483-491) as evidenced by 5,776,488. Note US '488 is only relied upon to show the inherent property claimed in claims 72 and 95.

Hanes et al teach aerodynamically light particles for drug delivery to the pulmonary system. The particles have a tap density of less than 0.4 g/cm3, aerodynamic diameter of 3

microns (see column 9, line 45-50), and a mass mean diameter (geometric diameter) between 5 to 30 microns. See abstract, See column 9, lines 26-45, and claim 1. Claim 3 teaches a tap density of less than 0.1 g/cm3. Table 2 teaches the porous microparticles with DPPC (phospholipids) have a density of 0.30 g/cm3. It should be noted that Hanes teaches tap density is a standard measure of the envelope mass density (bulk density) on column 9, lines 5-6. On column 14, lines 36-40, Hanes teaches the bulk density is estimated by tap density measurements.

Hanes teaches the presence of irregular surface structure, or pores or cavities within the particle (this reads on instantly claimed "hollow microstructure") contributes to the aerodynamic lightness. Hanes also teaches the irregular surface texture and porous structure also contributes to the low tap density and manipulation of these features permits the delivery of larger particle envelope volumes into the lungs (col. 9, lines 10-25). Porosity and surface roughness can be increased by varying the inlet and outlet temperatures, among other factors. See column 12, lines 10-13. The aerodynamically light particles may be fabricated to provide a particle sample with a preselected size distribution. For example, greater than 30%, 50%, 70%, or 80% of the particles in a sample can have a geometric diameter within a selected range of at least 5 microns. The particles contain surfactants such as DPPC (instant gel to liquid temperature; see US 5,776,488 as art of interest) and the microstructures are taught to encapsulate active agents, which allows the active to remain protected (col. 10, lines 37-50 and examples). Note that DPPC is a zwitterionic lipid. The particles can also be co-delivered with larger carrier particles, not carrying a therapeutic agent, having, for example, a mean diameter ranging between about 50 microns and 100 microns. See column 4, lines 12-15.

Biodegradable polymer, copolymers, or a blend may be utilized. Hanes teaches the use of polyglycolic acid and polylactic acid with a surfactant (DPPC) may be utilized and the polyester may also have a charged or functionizable groups such as amino acids. Other polymers taught are acrylic acids and methacrylic acids and polyvinyl compounds may be used to make the microsphere. See column 5, line 49 to column 6, line 27. Hanes teaches the particles may be made of the phospholipids (surfactants) and active. See claim 1 and column 5, lines 58-60. Further, the particles may be formed into microspheres by various methods including but not limited to coacervation, interfacial polymerization, etc. (note col. 6). Instant therapeutic agents including insulin, growth hormones, etc. are taught on column 10, lines 4-30.

Hanes teaches aerodynamically light PEG particles were prepared by spray drying using 5 g PEG (MW 15,000-20,000, Sigma) and the surfactant such as DPPC may be incorporated into the polymer solution prior to particle formation, or optionally the particles can be ionically or covalently coated by surfactant on the particle surface after particle formation, or the surfactant may be absorbed onto the particle surface. See column 13, lines 1-25. Note that when DPPC is incorporated into the polymer solution to form the particles, DPPC is part of the structural matrix.

Hanes et al do not teach the use of calcium in the structural matrix.

Papahadjopoulos et al teaches adding calcium to fuse phospholipids including the phosphoplipids taught by Hanes into larger vesicles. The reference teaches small vesicles with a size of 200-500 A in diameter can be made into bigger vesicles of a size of 0.2-1 micron. The reference teaches using calcium to form the desired size of the vesicle. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hanes and Papahadjopoulos and utilize calcium. One would be motivated to do so with the expectation of similar results since Hanes teaches the use of phospholipids only to form the particles and Papahadjopoulos teaches the use of calcium provides the desired vesicle size. Therefore, a skilled artisan would have been motivated to use the desired concentration of calcium to provide the desired lipid vesicles size. Note that the amount of calcium used provides the desired size as taught by Papahadjopoulos. Papahadjopoulos teaches forming bigger vesicles of a size of 0.2-1 microns in diameter and applicant claims a size of 1-30 microns.

With regard to the claims 4-5 (porosity), claims 6-7 (pore size), and claim 13 (shell thickness), although Hanes does not specify the porosity in terms of weight percent as instantly claimed, specify the pore size, or the shell thickness, it is the examiner's position that the Hanes would have a similar porosity, pore size, and shell thickness as instantly claimed for the following reason: Hanes teaches a substantially similar particle with instant bulk density (measured by tap density), instant geometric diameter, and instant aerodynamic diameter. Thus, "when a structure recited in the reference is substantially identical to that of the claims, claimed properties are presumed to be the inherent". See MPEP 2112.01. Further, Hanes teaches the porous and light nature of the microstructure contributes to the properties such as the low tap density of the particle and Hanes teaches the same density as claimed; thus the pore size and porosity must be similar as instantly claimed. Further, since the shell thickness also would contribute to the density of the particles and the prior art teaches the same density as claimed, it is the examiner's position that the prior art would have the same shell thickness as claimed. It

should be noted that the examiner has provided a rationale as to why Hanes's particle would have the same or similar porosity, pore size, and shell thickness; thus the burden has shifted to the applicant to provide evidence to the contrary. See MPEP 2112.

Furthermore, assuming arguendo that Hanes's porosity, pore size, and shell thickness are not the same as instantly claimed, the manipulation of these parameters is considered prima facie obvious to one of ordinary skill in the art since Hanes provides the guidance in which the various factors can be manipulated (column 9 and examples) to yield the desired property. For instance, Hanes teaches manipulating the outlet and inlet temperature when making the particles to manipulate the porosity. Further, Hanes teaches the manipulation of surface roughness (porosity), diameter, and tap density, determine the delivery site of the particles in the lungs (lower lung region or upper lung region). (col. 8, lines 19-68 and column 9). Therefore, a skilled artisan would have been motivated to look at the guidance of Hanes and manipulate the above factors and fabricate the microstructure according to the lung region to be targeted.

Regarding the claim language of 58 and 81, Note MPEP 2111.03: The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." The examiner also points out that Hanes teaches the particles may be made of the surfactant, i.e. phospholipids.

Claims 78 and 101 are under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Mathiowitz et al (6,248,720) or Cohen et al (5149543) or

Papahadjopoulos et al (Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biophysics, 394 (1975), 483-491) *respectively* in further view of Igarashi et al (4201774).

The detailed teaching of Hanes, Mathiowitz, Cohen, Paphadjopoulos have been set forth above. Hanes et al teach dry powder inhaler compositions. Hanes teaches several active agents including antibiotics in the composition.

Hanes does not teach the specific use of aminoglycoside antibiotic.

Igarashi et al teaches aminoglycoside antibiotics for the treatment of gram-positive and gram-negative bacteria.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the instant medicament in Hanes et al's composition. One would be motivated to do so since the instant antibiotics treats gram-positive and gram-negative bacteria and depending on the patient's requirement, the appropriate drug is used. One would have expected similar results since Hanes teaches the suitability of antibiotics as the active agent. Therefore, the selection of a particular drug for use in the composition is considered prima facie obvious since the selection depends on the symptoms and disease being treated.

Claims 79 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Mathiowitz et al (6,248,720) or Cohen et al (5149543) or Papahadjopoulos et al (Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biophysics, 394 (1975), 483-491) *respectively* in further view of Benson et al (5,006,343).

The detailed teaching of Hanes, Mathiowitz, Cohen, Paphadjopoulos have been set forth above. Hanes et al teach dry powder inhaler compositions. Hanes teaches several active agents including antibiotics in the composition.

Hanes does not teach the specific use of fungicides.

Benson et al teach pulmonary administration of active agents to treat pulmonary diseases. Suitable drugs that may be administered for lung specific disease include fungicides. See column 10, lines 33-45.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a fungicide in Hanes et al's composition. One would be motivated to do so since Benson et al teach the use of array of medications including fungicides that are useful for treating lung diseases. Therefore, the selection of a particular drug for use in the composition is considered prima facie obvious since the selection depends on the symptoms and disease being treated.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of claims 4-15, 18-23, 39-40, 42-47, and 49-56 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 8-9, 11-15, 17, 19-25, 29-32, 53-55, 57-62, 64-66, 67-89 of copending Application No. 09/851226 is withdrawn since the application has been abandoned.

Claims 4-15, 18-23, 39-40, 42-47, and 49-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-7, 9-10, 46-50, 54-57, 59, 61-67, 69-70, 74-77, 79-90 of copending Application No. 09/568818. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant application claim 39 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3, and an aerodynamic diameter of less than 5 microns. Independent claim 40 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antifungals, insulin, etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

Copending independent claims 46, 59, and 82 are directed to a microparticle comprising an active agent and a metal-ion complex with a density as measured by He displacement is 0.5-2 g/ml. Calcium is one of the metal ion species claimed in a dependent claim. Dependent claims are directed to phospholipids and specifically selected from the group comprising "dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, and dimyristylphosphatidylcholine". Dependent claims are directed to the same active agents as claimed in instant application. Dependent claims are directed to an aerodynamic particle size of 0.5-7 microns. Dependent claims are directed to dry powder. Dependent claim are directed to a zwitterionic lipid.

The instant application and '818 are different in that firstly '818 independent claims do not recite a phospholipid; however the dependent claims further comprise phospholipids, more specifically, the instant phospholipids. Thus, the instant application and copending application have overlapping subject matter wherein both application are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion. Secondly, '818 is directed to the broad scope of the metal ion and the instant application is directed to the metal ion species calcium; however, '818 claims calcium in the dependent claims. Further, '818 is broadly directed to microparticles without claiming the density, the geometric diameter, pore size, etc.; however '818 encompasses the scope of the instant microstructures and the respective properties, which is the narrower scope. Lastly, it should be noted with regard to instant claim 40, although '818 does not specifically claim "phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius", '818 does claim DPPC in the dependent claims and DPPC has a temperature of 42 degrees Celsius.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 4-15, 18-23, 39-40, 42-47, and 49-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15, 19-22, 37-49, 52-64, 67-79, 82-83, 94, and 102 of copending Application No. 10/750934. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant application claim 39 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3, and an aerodynamic diameter of less than 5 microns. Independent claim 40 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antineoplastics, antifungals, specifically insulin, growth factors etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

'934 is directed to a pharmaceutical composition comprising particles comprising an active ingredient in a lipid matrix. The particles have a geometric diameter of less than 3 microns and a mass median diameter of less than 20 microns. Dependent claims are directed to a lipid selected from dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine,

dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine. Dependent claims are directed to hollow, porous particles with a bulk density of less than 0.5 g/cm3, 0.3 g/cm3, and 0.2 g/cm3. Dependent claims are directed to the particle further comprising a polyvalent cation and the specification defines the polyvalent cation as calcium, magnesium, and iron. Independent claim is directed to a specific active agent, amphotericin.

Copending application and instant application are different because '934's independent claim is not directed to a metal ion. However, the independent claims have comprising language and the dependent claim is directed to the particle further comprising polyvalent metal ions. Thus, the combination of a polyvalent ion, phospholipid, and active agent renders a scope that encompasses the scope of the instant application. Thus, both application are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion.

Claims 4-15, 18-23, 39-40, 42-47, and 49-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27, 32-39 of copending Application No. 10/982191. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant application claim 39 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3, and an aerodynamic diameter of less than 5 microns. Independent claim 40 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature

of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antineoplastics, antifungals, specifically insulin, growth factors etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

'191 is directed to a pharmaceutical composition comprising active ingredient and a lipid wherein the gel to liquid crystal transition temperature of greater than 57 degrees Celsius. The dependent claims are directed to the lipid components selected from dipalmitoylphosphatidylcholine. Dependent claims further comprises a divalent cation, specifically calcium. Dependent claims are directed to composition in a dry powder form wherein the particles are hollow and porous particles. Dependent claims are directed to the particles having a geometric diameter of less than 20 microns. Dependent claims are directed to the particles with a bulk density of less than 0.5 g/cm3, 0.3 g/cm3, and 0.2 g/cm3.

Copending application and instant application are different since '934's independent claim is not directed to a metal ion. However, the independent claims have comprising language and the dependent claim is directed to the particle further comprising polyvalent metal ions, specifically calcium ions. Thus, the combination of a polyvalent ion, phospholipid, and active agent renders a scope that encompasses the scope of the instant application. Thus, both application are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion.

Response to Arguments

Applicant states that the rejections will be addressed upon indication of allowable subject matter. Therefore, the rejection s are maintained for the reasons stated above.

Pertinent Prior Art

PGPUB 20020052310 with an effective filing date of 12/29/00 and claiming benefit to US provisional 60/05004 filed 9/15/97 is considered pertinent to applicant's disclosure but does not constitute prior art since the pertinent subject matter regarding divalent cations in section [0093] is not supported in the provisional application of 60/05004. The subject matter claimed in the instant application is supported in US provisional application 60/060337 which has a filing date of 9/29/97.

Conclusion

All the claims are rejected at this time

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila Gollamudi Landau whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sharmila Gollamudi Landau
Primary Examiner
Art Unit 1616

10/27/07